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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/712,259 | 11/14/2003 | Elaine Merisko-Liversidge | 029318-0979 | 8061 |

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| EXAMINER | |
|---|---|
| CHANNAVAJJALA, LAKSHMI SARADA | |
| ART UNIT | PAPER NUMBER |
| 1611 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/712,259 | MERISKO-LIVERSIDGE, ELAINE | |
| | Examiner | Art Unit | |
| | Lakshmi S. Channavajjala | 1611 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-15,17,18 and 24-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15,17,18 and 24-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-11-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Reciept of IDS, amendment and response dated 12-11-07 is acknowledged.

Claims 1, 3-15, 17-18 and 24-39 are pending in the instant application. Claims 2, 16, 19-23 and 40-93 have been canceled.

**Examiner clarifies that the election of species requirement between the surface stabilizers and the particle sizes required by the Restriction Requirement dated 1-9-06 is no longer maintained. All of the instant claims require that the particle size is less than 1000 nm. Accordingly, the species election of the phases of nifedipine and the non-nifedipine agents (explained on page 7-10) of the office action dated 1-9-06 have been maintained.**

In response to the amendment, the following new rejection has been applied:

***Claim Rejections - 35 USC § 103***

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1, 3-15 and 24-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,566,081 to Doi et al (Doi) in view of US 5,145,684 to Liversidge et al (Liversidge) OR unpatentable over EP0220760 (EP) in view of Liversidge.

3. Doi teaches solid nefidipine preparations as vasodilating agents with excellent dissolution and control over the dissolution rate, by pulverizing the drug together with the excipients in to very fine particles. The composition comprises particulate nifedipine obtained by two methods i.e., co-pulverization of nefidipine in mixture with casein and inorganic excipients or co-pulverization of a high molecular substance and a plasticizer with a higher fatty acid ester (col. 3, L 45-67). For the enteric high molecular weight substance, Doi teaches compounds such as cellulose acetate, hydroxypropylmethylcellulose phthalate, plasticizer including polyethylene glycol, polyoxyethylene sorbitan monooleate etc (col. 6, L24-54). Doi teaches that the dissolution rate can be controlled by adjusting the amount of fatty acid ester (table 1, fig. 6). The plasticizer taught by Doi read on the instant surface stabilizers of claims 1, 10 and 11. The solid formulation of Doi reads on the instant controlled released formulation and further Doi teaches capsules containing nifedipine, thus reading on claims 5. Table 1 of Doi shows the amount of nifedipine and the other compounds that read on the amounts of claims 6 and 7. Doi teaches crystalline nifedipine particles (col. 5, L 2-10), but not the claimed particle sizes.

4. EP teaches solid nifedipine formulations of high bioavailability and consists of active agent (nifedipine) together with a polyethylene glycol. EP teaches that the co-precipitation of nifedipine with PEG allows the drug to absorb on the surface of the PEG and thus allows for the formation of very fine dispersion of particles. EP suggests that the same can be achieved with the intimate blending of the PEG with nifedipine

(abstract, page 2 and L 38-54). For the amounts of PEG, nifedipine, see page 3. In addition, EP also suggests including other compounds such as HPMC, gums, carboxy vinyl polymers etc., for increasing the retardant effect of the tablet preparation containing nifedipine and PEG (page 3, L 20-28). EP teaches preparing fine particle sizes of nifedipine but fails to state the actual particle sizes of the instant claims.

5. Liversidge teaches preparation of nanoparticulate drug compositions in which the drug is surface modified by addition of one ore more surface stabilizers. Liversidge teaches that the rate of a dissolution of a particulate drug increases with increasing surface area (decreasing particle size) (col. 1) but states that conventional techniques to reduce the particle sizes have limitations such as toxicity of the solvents used. In order to improve the stability of the dispersed particles, without flocculation, Liversidge suggests wet milling and grinding in conjunction with a surface modifier and further states that such grinding would render the particles crystalline with the surface stabilizer absorbed on the particles (col. 2 & 3). Liversidge teaches preparing particles of less than 400 nm (col. 2). Liversidge suggests employing the process of preparing particles for a number of poorly soluble drug substances and include several classes of drugs include g vasodilators (lines bridging col. 3-4)., Liversidge teaches all of the surface modifiers that are disclosed and claimed in the instant application (col. 4, L 34-13 and examples ).

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to reduce the particle size of nifedipine and prepare

crystalline nifedipine nanoparticles having a particle size of 400 nm or less in the compositions of Doi or EP because Liversidge teaches that the wet milling and grinding of poorly water soluble drugs together with any of the surface stabilizers (see examples of Liversidge) results in the stability of the insoluble drug particles and Liversidge further states that the compositions also exhibit unexpectedly high bioavailability. Accordingly, preparing a nanoparticulate nifedipine composition in the teachings of Doi or EP would have been within the scope of a skilled artisan. For claims 24-28, both the compositions (Doi and EP) exhibit the property because according to the instant specification, the nanoparticle nifedipine exhibits redispersion upon administration at a biorelevant pH, which is stomach pH ([0066 and 0067]).

6. Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,566,081 to Doi et al (Doi) in view of US 5,145,684 to Liversidge et al (Liversidge) OR unpatentable over EP0220760 (EP) in view of Liversidge as applied to claims 1, 3-15 and 24-39 above, and further in view of US 4,814,175.

Doi, EP and Liversidge fail to teach the combination of nifedipine and cardiovascular agents.

175 teach a combination of particulate nifedipine and a beta-blocker for treating cardiovascular diseases, and states that a combination allows for a reduced dose of nifedipine and affords an advantage over a conventional preparation i.e., provides a

prolonged therapy for a 24-hour period. '175 also teach preparing solid dosage forms such as tablets or capsules.

Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to combine nifedipine of Doi or EP with other therapeutic compounds such as beta blockers and also prepare the nanoparticulate nifedipine of Doi or EP, as tablets or capsules (solid) because '175 suggests a combination therapy of nifedipine and beta blocker and one of an ordinary skill in the art would have expected to treat cardiovascular diseases with a lower amount of nifedipine and for a prolonged period.

***Claim Rejections - 35 USC § 112***

7. Claim 11 recites the limitation "polyvinylpyrrolidone" in line 11. There is insufficient antecedent basis for this limitation in the claim.

***Response to Arguments***

***8.*** Applicant's arguments see pages 13-16, filed 12-11-07, have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as above.

***Conclusion***

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. US 4,562,069 to Hegasy et al.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner,
Art Unit 1611
March 8, 2008